EXHIBIT 5
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(54) Title: STABLE COMPOSITIONS CONTAINING N-PROPARGYL-1-AMINOINDAN

(57) Abstract

A pharmaceutical composition comprising as active ingredient a racemic, S(-), and R(+)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof, and at least 60 % by weight of at least one pentahydric or hexahydric alcohol. Optionally the composition may contain citric acid and magnesium stearate.

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STABLE COMPOSITIONS CONTAINING N-PROPARGYL-1-AMINOINDAN

FIELD OF THE INVENTION

The present invention concerns formulations of racemic, S(−) or R(+) enantiomers of N-propargyl-1-aminoindan, and especially formulations of the enantiomer R(+) of N-propargyl-1-aminoindan (referred to hereinafter as R(+) PAI) which is a selective irreversible inhibitor of the B-form of the enzyme monoamine oxidase used, for example, for the treatment of Parkinson's disease. In the following the enzyme monoamine oxidase will be referred to as MAO and the B-form thereof as MAO-B.

BACKGROUND OF THE INVENTION

GB 1 003 686 discloses a group of benzocycloalkane compounds in which the cycloalkane has from five to seven ring members and is substituted by an N-(alkynylalkyl)amino group, and their use as MAO inhibitors. The patent further discloses the use of the subject compounds in admixture with a variety of substances including various alcohols such as a benzyl alcohol, stearyl alcohol, and methanol. The patent, however, does not teach how and by what criteria any of the many possible carriers and other ingredients are selected so as to overcome the stability problem of the product.

The object of the present invention is to provide stable formulations comprising an effective amount of racemic, S(−) or R(+)−N−propargyl−1−aminoindan. For the sake of simplicity, the abbreviation PAI, unless specified otherwise, will be used to denote the enantiomers of N−propargyl−1−aminoindan, as well as their racemic mixtures.

SUMMARY OF THE INVENTION

In accordance with the invention it was surprisingly found that the stability of formulations comprising PAI can be significantly improved by the incorporation of relatively large amounts of certain alcohols.

In accordance with the present invention there is provided a pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound being a member selected from the group of racemic, S(−), and R(+)−N−propargyl−1−aminoindan or a pharmaceutically acceptable salt thereof, and at least 60% by weight of at least one alcohol being a member selected from the group of pentahydric and hexahydric alcohols.

In a preferred embodiment of the present invention the active ingredient is R(+)−N−propargyl−1−aminoindan.

Preferably the composition comprises at least 70% of said at least one alcohol.

Typically the alcohol used in accordance with of the invention, is a member selected from the group of mannitol, xylitol and sorbitol.

In accordance with the invention the PAI−comprising composition may further include citric acid, preferably in an amount of 0.5 to 2% by weight.

If desired, compositions according to the invention may further comprise magnesium stearate, preferably in an amount of 0.1 to 0.5% by weight. According to this embodiment, where the amount of said at least one alcohol is less than 70% by weight, the composition further comprises citric acid in an amount specified above. Where the amount of said at least one alcohol is at least 70% by weight, the inclusion of citric acid is optional.

The composition of the present invention may optionally also include conventional additives such as fillers, lubricants, disintegrants, glidants, flavoring agents, sweeteners, coloring agents, and the like, all as known *per se*. Examples of fillers which may be used in accordance with the present invention are lactose, starch, microcrystalline cellulose, maltrin and the like.

The compositions of the present invention may be prepared by methods known *per se*, familiar to those skilled in the art. For example, PAI and all other ingredients (with the exception of the lubricant, when used) may be screened and mixed thoroughly in a suitable granulating machine. The granulation may occur in the presence of purified water, following which the composition is dried. The dry granulate may then be milled, lubricated and compressed into tablets. R(+) PAI itself may be prepared, for example, according to the process described in Example 6B of WO95/11016.

The following non-limiting examples are given by way of illustration.

EXAMPLES

EXAMPLE 1

	mg/tablet
R(+)-N-propargyl-1-aminoindan mesylate	3.12
Mannitol	62.5
Maltodextrin (Maltrin 150)	36.0
Croscarmellose sodium (Ac-Di-Sol)	2.1
Talc	1.5

EXAMPLE 2

	mg/tablet
R(+)-N-propargyl-1-aminoindan mesylate	1.56
Mannitol	79.14
Starch	10.0
Pregelatinized starch	10.0
Colloidal silicon dioxide	0.6
Talc	2.0
Stearic acid	2.0

EXAMPLE 3

	mg/tablet
R(+)-N-propargyl-1-aminoindan mesylate	3.12
Mannitol	76.58
Starch	10.0
Pregelatinized starch	10.0
Colloidal silicon dioxide	0.6
Citric acid	1.0
Talc	2.0

EXAMPLE 4

	mg/tablet
R(+)-N-propargyl-1-aminoindan mesylate	3.12
Mannitol	69.88
Lactose (hydrous)	14.0
Starch	14.0
Glyceryl Behenate (Compitrol 888 ATO)	2.0

EXAMPLE 5

	mg/tablet
R(+)-N-propargyl-1-aminoindan mesylate	3.12
Mannitol	77.28
Starch	10.0
Starch STA-RX 1500	10.0
Colloidal silicon dioxide, Aerosil	0.6
Hydrogenated vegetable type I (Sterotex Dritex)	2.0

EXAMPLE 6

In order to compare the compositions of the present invention with those known in the prior art, two of the above formulations were compared with a formulation described in WO95/11016.

Formulation of WO95/11016 (Example 20)

	mg/tablet
R(+)-N-propargyl-1-aminoindan HCl	1.56
Lactose (hydrous)	50.0
Pregelatinized starch	36.0
Microcrystalline cellulose	14.0
Sodium starch glycolate	2.14
Talc	1.0
Magnesium stearate	0.5

This formulation, as well as those described under Examples 2 and 3 of the present application were subjected to 6 months at 40°C and 75% humidity. The percentage of degradants of the active material was assayed at the end of the six month period.

The following procedure was adopted to determine the degradation of the formulations prepared. The tablets were finely powdered and extracted with a diluent such as a mixture of water, acetonitrile and perchloric acid. An aliquot of the extraction product was injected into an HPLC and eluted using the same mixture as said diluent mixture. The area corresponding to the PAI compound was determined as was that of any other major peak. The calculations of degradation percent was made by comparing the areas of the measured peaks with those obtained from the standard preparation.

It was found that the formulation prepared according to the disclosure of Example 20 of WO95/11016 contained after storage 3.08% degradants whereas the formulations of Examples 2 and 3 contained 0.51% and less than 0.1% degradants, respectively.

EXAMPLE 7

Formulations according to the present invention and others according to the description given in Example 20 of WO95/11016 were prepared containing the ingredients shown in Table 1. The formulations described in this Table are designated "PCT" when prepared in accordance with the disclosure in WO95/11016, or by a number which corresponds to the number of the Example in the present application, in which they are described. The qualifying symbols of A, B, C or D appearing next to some of these designations denote certain variations in said formulations. The percentage of degradation, presented in Table 2, was calculated for all the formulations of Table 1, after storing them for 1 month at 55°C or for 6 months at 40°C and 75% humidity. Those formulations stored according to the latter storing conditions are marked in the Table with an astrix (*). As can be seen from Table 2, the stabilities of all the compositions of the present invention was superior to those of the prior art.

TABLE 1

Example No.	PCT mg	PCT-A mg	PCT-B mg	PCT-C mg	1 mg	1A mg	1B mg	1C mg	1D mg	2 mg	2A mg	3 mg	3A mg	4 mg	5 mg	5A mg	5B mg	5C mg	8 mg	9 mg
N-Propargyl-1(R)-Aminoindan Mesylate	1.56	5.0	1.0	7.81	3.12	3.12	1.56	3.12	1.56	1.56	1.56	3.12	1.56	3.12	3.12	1.56	1.56	1.56	1.56	1.56
Mannitol USP					62.5	62.5				79.14	78.44	76.58	77.44	69.88	77.28	78.87	78.87	78.87		
Starch STA-RX 1500	36.0	47.0	36.0	47.0			36.0	36.0	36.0	10.0	10.0	10.0	10.0		10.0	10.0	10.0	10.0	10.0	10.0
Starch NF Starch NF (in paste)										5.6 4.4	10.0	5.6 4.4	10.0	14.0	10.0	10.0	10.0	10.0	10.0	10.0
Colloidal Silicon Dioxide (Aerosil 200)										0.6	0.6	0.6	0.6		0.6	0.6	0.6	0.6	0.6	0.6
Citric acid								1.0	2.0			1.0	1.0							
Talc USP	1.0	1.5	1.0	1.5	1.5	1.5	1.0	1.0	1.0	2.0	2.0	2.0	2.0			2.0	2.0	2.0	2.0	2.0
Microcrystalline Cellulose (Avicel 102)	14.0	20.0	14.0	20.0			14.0	14.0	14.0											
Stearic acid NF							2.0			2.0	2.0	2.0	2.0			2.0		2.0	2.0	2.0
Lactose NF Hydrous	50.0	66.0	50.0	66.0			50.0	47.44	46.44					14.0						
Sodium Starch Glycolate	2.14	3.0	2.2	2.99			2.14	2.14	2.14											
Magnesium Stearate	0.5	0.7	0.5	0.7		0.52	0.1	0.5	0.5							0.1	0.5	0.5		
AC-DI-SOL					2.1	2.1														
Lactose spray dried																				
Compritol 888 ATO																				
Maltrin					36.0	36.0								2.0						
Sorbitol																			78.84	
Xilitalo 300																				78.84
Sterotex - Ditex															2.0					
Total Weight(mg)	105.2	143.2	104.7	146.0	105.22	105.74	106.8	105.2	105.2	105.3	104.6	105.3	104.6	103.0	103.0	105.13	103.53	105.53	105.0	105.0

Table 2

Example No:	% Degradants	Mannitol (%)	Sorbitol (%)	Xylitol (%)	Magnesium stearate (%)	Citric acid (%)
PCT(*)	2.26	-			0.5	-
PCT-A	2.76	-			0.49	-
PCT-B	1.46	-			0.49	
PCT-C(*)	2.59	-			0.5	-
1	1.22	59.4			-	-
1A	3.97	59.1			0.49	-
1B	2.04	-			0.1	-
1C	1.04	-			0.47	0.95
1D	0.40	-			0.47	1.9
2	0.29	75.1			-	-
2A	0.27	75				
3	0.02	72.7			-	0.95
3A	0.02	74				0.95
4	0.02	67.8			-	-
5	0.21	75			-	-
5A	0.32	75			0.1	-
5B	0.65	76.2			0.47	-
5C	0.52	74.7			0.47	-
6	0.74		75.1		-	-
7	1.01			75.1	-	-

CLAIMS:

1. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound being a member selected from the group of racemic, S(−), and R(+)−N−propargyl−1−aminoindan or a pharmaceutically acceptable salt thereof, and at least 60% by weight of at least one alcohol being a member selected from the group of pentahydric and hexahydric alcohols.

2. A pharmaceutical composition according to Claim 1, comprising at least 70% by weight of said at least one alcohol.

3. A pharmaceutical composition according to Claim 1 or 2, wherein the said at least one alcohol is a member selected from the group of mannitol, xylitol and sorbitol.

4. A pharmaceutical composition according to any one of claims 1 to 3, further comprising citric acid.

5. A pharmaceutical composition according to Claim 4, wherein the amount of citric acid is 0.5 to 2% by weight.

6. A pharmaceutical composition according to any one of claims 1 to 5, further comprising magnesium stearate.

7. A pharmaceutical composition according to Claim 6, wherein the amount of magnesium stearate is 0.1 to 0.5% by weight.

8. A pharmaceutical composition according to Claim 6 or 7 in which the amount of said at least one alcohol is 70% or less, further comprising citric acid.

9. A pharmaceutical composition according to any one of the preceding claims, wherein said active ingredient is R(+)−N−propargyl−1−aminoindan.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL96/00115

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/135
US CL :514/647

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/647

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 3,513,244 A (GITTOS ET AL.) 19 May 1970, see column 1, line 70 and column 5, lines 4-10.	1 and 3 --- 1-3
Y	US 5,387,612 A (YOUDIM ET AL.) 07 February 1995, see the abstract, column 5, lines 65-68, column 6, lines 3-6 and column 10, Example 15.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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Date of the actual completion of the international search
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL96/00115

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.